

LETTER TO THE EDITOR

Problems with paper entitled *The impact of tacrolimus exposure on extrarenal adverse effects in adult transplant recipients*

I read with interest the paper entitled *The impact of tacrolimus exposure on extra-renal adverse effects in adult renal transplant recipients* that was published in the *Journal* (2019, Vol 85, pp. 516–529).

The authors of this paper investigated potential links between a 12-hour exposure to tacrolimus (measured via the AUC₀₋₁₂ at ≥ 6 mo post-transplant) and compared this with reported adverse effects (AEs) including cosmetic, neurological and gastrointestinal effects.

I have several concerns with this paper including:

- 1) Mechanistically, some AEs are more likely to be related to immediate exposure (e.g. gastrointestinal effects that are related to drug concentration at the mucosal surfaces) while others are more likely to result from accumulation in affected tissues (e.g. nephrotoxicity and neurological AEs). The study design in this paper is interesting in this regard because the authors appear to have assumed that a single 12-hour exposure calculated at a single time point many months distant from the initiation of tacrolimus is the same as (or at least reflective of) cumulative exposure.

The authors advise (Table 1) that the median time post-transplant was 2.2 years but that the range was 0.6–14 years and this guarantees a huge interpatient variability in cumulative tacrolimus exposure in these 67 kidney transplant recipients. The authors also do not provide data on when the AEs first became evident relative to tacrolimus' initiation and although they note this briefly in their *limitations* (p. 526), I think this is a severe limitation in this study's design that attempted to ascribe AEs to *exposure* to tacrolimus.

- 2) The authors gave no information as to how their 67 subjects were recruited. If they were recruited because they had reported AEs this would introduce a selection bias.
- 3) The authors advise (Table 1) that 20.9% of the subjects were prescribed prednisone in addition to tacrolimus and mycophenolate. Several of the AEs of interest to the authors can be caused (or aggravated) by the use of this steroid, including gastrointestinal upsets (especially dyspepsia requiring acid suppressive therapy), acne and other skin changes, myopathy, diabetes, and cholesterol changes. Transplant rejection is frequently treated by corticosteroids and it is possible that many more of the cohort had received prednisone at an earlier time and that this had contributed to the AEs counted at the time of the study. I

was disappointed to not see any mention of this as a confounder and no separate analysis of AEs relative to cumulative prednisone use. This is another major limitation to this study's design/findings.

- 4) The authors *dose-normalised* both AUC and Cmax metrics in their correlations with AEs. In the *Introduction* they advise that they were intending to "investigate whether standardized extrarenal AEs are associated with tacrolimus exposure" but by dose-normalising AUC, the remaining metric is no longer an estimate of exposure but rather it is a measure of (the inverse of) clearance. Similarly, dose-normalizing Cmax no longer provides a measure of (maximal) exposure but of (the inverse of) volume of distribution. This is evident from the equation (AUC = Dose/(CL/F)) on page 519 and from the units used in the vertical (Dose normalized Tacrolimus AUC) axis in Figure 1. The authors also advise "Dose-normalized tacrolimus AUC_{ss0-12h} and apparent clearance were independently associated with diarrhoea, dyspepsia, insomnia and neurological AE ratio" (Results in Abstract) which is hardly surprising since they are effectively the same measure! That this is repeated in the main text "Logistic regression identified tacrolimus dose-normalized AUC_{ss0-12} and dose-normalized Cmax with apparent clearance (Cl/F) to be significant predictors for adverse events" (p. 52 under Results) and elsewhere in the paper, suggests the authors were not aware that the "dose normalised AUC" is effectively the same as clearance.

The authors observe that "This dose normalization enables comparison between different stable regimens" (p. 521) but I find this implausible since the metrics they used did not estimate exposure. Patients receiving tacrolimus have their doses individualized (based upon tacrolimus trough concentration) and this (at least partially) *normalizes* exposure to account for differences in patient factors. Given the well-known variabilities in absorption and clearance, the appropriate pharmacokinetic metric for interpatient comparisons with tacrolimus and AEs should surely be the unadjusted AUC/Cmax. I would like to know why the authors did not use these measures in their analyses.

- 5) In Figure 1, the authors have incorrectly used the same units for Dose normalized Tacrolimus AUC as for Dose normalized Tacrolimus Cmax—the units for the latter should surely be "ng. mL⁻¹.mg⁻¹".

It is difficult to imagine (mechanistically) how the inverse of clearance or Vd could be associated with the AEs reported. Given these methodological flaws, I suspect that the associations found in this paper were more by chance than the exposure metrics the authors suggest.

COMPETING INTERESTS

There are no competing interests to declare.

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